are objected to for being dependent on a rejected claim. Reconsideration of this application in light of the following remarks is respectfully requested.

Rejection under 35 U.S.C. 102(b)

Claims 1-3, 5, 8, 14-17, 21 and 27 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Schantz et al., *J. AOAC* 61:96-99 (1978) ("Schantz"). The Office Action states that Schantz teaches a solvent composition comprising purified botulinum type A toxin in acetate buffer having a pH of 4.2 for at least two years at room temperature, preferably 18-24°C. The Office Action indicates that pH 4.2 is "about 5" and that "room temperature falls between the claimed range of 10-30°C or even between 0-10°C based on location, is inherent from the teaching of the prior art." This rejection is respectfully traversed.

It is well established law that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *See Verdegaal Bros. V. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claim 1 is directed to a stable liquid pharmaceutical botulinum toxin formulation comprising a pharmaceutically acceptable buffer capable of providing a buffered pH range between about pH 5 and pH 6, and purified botulinum toxin, wherein the formulation is stable as a liquid for at least one year at a temperature between about 0°C and 10°C. Claim 16 is directed to a stable liquid pharmaceutical botulinum toxin formulation comprising a pharmaceutically acceptable buffer capable of providing a buffered pH range between about pH 5 and pH 6, and purified botulinum toxin, wherein the formulation is stable as a liquid for at least one year at a temperature between about 10°C and 30°C.

A close reading of Schantz does not teach a stable liquid pharmaceutical botulinum toxin formulation as claimed in Claim 1 or Claim 16. Schantz only teaches

two formulations (noted and referred to as (A) and (B) below), both having a pH outside of the range of between about pH 5 and pH 6 as claimed in Claim 1 and 16. Further, both of the Schantz formulations have stability problems, namely loss of toxicity if frozen (pH 4.2) or loss of toxicity at room temperature (pH 6.2). Both of these problems have been solved by the formulations of Claims 1 and 16. The two Schantz formulations are as follows:

Schantz Formulations

(A) At page 96-97: "...pH 4.2 sodium acetate buffer containing 3 mg bovine serum albumin and 2 mg gelatin/ml...The solution should be stored at room temperature (preferably 18-24 °C), but *must not be frozen or the toxicity will be destroyed...*", and at page 98 (column 2), "[o]ne disadvantage to dissolving the toxin in pH 4.2 acetate buffer is that *it cannot be frozen without loss of toxicity...*" (emphasis added).

(B) At page 97: "...[s]terile sodium phosphate buffer...pH 6.2, containing 0.2% gelatin...", and at page 98 (column 2) "...in pH 6.2 sodium phosphate buffer...the solution can be frozen and thawed without appreciable loss of toxicity. However, the toxicity in phosphate buffer *at room temperature is not maintained more than a few days without considerable loss.*" (emphasis added).

Claim 1

Schantz does not teach each and every element of the invention of Claim 1. Schantz does not teach a stable liquid botulinum toxin formulation with the pH range of between about pH 5 and pH 6 that is stable for at least one year at a temperature between about 0-10°C. As noted above, Schantz teaches formulation (A) with pH 4.2 at room temperature preferably 18-24°C. A formulation with pH 4.2 at room temperature preferably 18-24°C does not anticipate a pH range of about pH 5 to pH6 at 0-10°C. Further, Schantz clearly states that a *disadvantage* to the pH 4.2 formulation is that it cannot be frozen without loss of toxicity, i.e. the fomulation is not stable for at least one year at a temperature between 0-10°C.

Schantz's formulation (B) above has a pH of 6.2, can be frozen and thawed without appreciable loss of toxicity, but the toxicity is not maintained at room temperature for more than a few days. A formulation with pH 6.2 does not anticipate a pH range of about pH 5 to pH 6.

Further, it is well known that pH is measured on a logarithmic scale and one skilled in the art would recognize that differences in pH affect the stability of a protein formulation. Thus, the Office Action incorrectly states on page 3, paragraph 10, that a pH of 4.2 is about pH 5.

Accordingly, Schantz fails to teach each and every element of Claim 1 and does not anticipate Claim 1.

Claim 16

Schantz fails to teach each and every element of Claim 16. Claim 16 is directed to a stable liquid botulinum toxin formulation having a pH range between about pH 5 and pH 6 that is stable for at least 6 months at a temperature between about 10-30°C.

Schantz's formulation (A) above has a pH of 4.2 and is stable at room temperature, preferably 18-24°C. A pH of 4.2 does not teach or describe a pH range of between about pH 5 and pH 6.

Schantz's formulation (B) above has a pH of 6.2, but the toxicity is not maintained at room temperature for more than a few days. The invention of Claim 16 is a formulation that is stable for at least 6 months at a temperature between about 10-30°C. A pH of 6.2 does not teach or describe a pH range of between about pH 5 and pH 6, nor does an unstable formulation at room temperature teach or describe a formulation stable for at least 6 months at a temperature between about 10-30°C.

Accordingly, Schantz fails to teach each and every element of Claim 16 and does not anticipate Claim 16.

Summary

In summary, each of the Schantz formulations have problems that have been solved by this invention. First, Schantz teaches formulation (A) having a pH 4.2 that is not stable when frozen. Claim 1 is directed to a formulation with a pH between about pH 5 and pH 6 that is stable for at least one year at 0-10 °C. Second, Schantz teaches formulation (B) having pH 6.2 that can be frozen but loses toxicity after a few days at room temperature (18-24°C). Claim 16 is directed to a formulation with a pH between about pH 5 and pH 6 that is stable for at least 6 months at a temperature between about 10-30°C.

Accordingly, it is respectfully submitted that Schantz does not teach each and every element and thus does not anticipate independent Claims 1 or 16. Accordingly, it is respectfully submitted that this §102(b) rejection is in error and it is respectfully requested that it be withdrawn against Claims 1-3, 5, 8, 14-17, 21 and 27.

Claim Objections

Claims 4, 6, 7, 9-13, 18-20, 22-26 and 28 are objected to for being dependent on a rejected claim. In light of the above remarks, it is respectfully submitted that this rejection is now moot and Applicants respectfully request that it be withdrawn.

Conclusion

For the reasons set forth above it is submitted that this case is now in condition for allowance. Early notice to that effect is respectfully requested.

Respectfully submitted,

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Leslie J. Boley
Registration No. 41,490
Tel. no. 650-866-2773

Customer no. 21835
Elan Pharmaceuticals, Inc.
800 Gateway Boulevard
South San Francisco, CA
94080